REMARKS

Reconsideration is requested.

Claims 15-17 and 20-43 are pending.

Claims 18 and 19 have been canceled, without prejudice.

The claims, including the withdrawn claims, have been amended pursuant to the format provided in the USPTO "flyer" - REVISED AMENDMENT PRACTICE: 37 CFR 1.121 CHANGED COMPLIANCE IS MANDATORY - Effective Date: July 30, 2003 (Rev.3 (07/24/03)). See, for example, Claims 7 and 8 of the Examples on page 2 of the "flyer".

Claim 43 has been added above based on unamended claim 40.

Claim 40 has been amended and claims 43 added to correct multiple dependencies. The Examiner's indication that claims 15-43 were pending as of the issuance of the Office Action dated January 15, 2004, is not understood and clarification is requested. Specifically, the Office Action of September 24, 2003 correctly indicated that claims 15-42 were pending and claims were not added in response to the Office Action of September 24, 2003. The above is submitted to be a correct listing of the claims. Clarification is requested however if the Patent Office believes otherwise.

The Examiner's consideration and examination of the subject matter of the Examiner's Groups I and II (as defined in the Office Action dated September 24, 2004) is acknowledged, with appreciation. The Examiner is again requested to also examine the subject matter of the Examiner's Group III with the subject matter of the Examiner's Groups I and II as allowability of the subject matter of the subject matter of Group II (as defined by claim 16 - "A therapeutic HCV vaccine composition comprising a

therapeutically effective amount of at least one HCV single or specific oligomeric envelope E1 protein or a part thereof; and at least one of a pharmaceutically acceptable carrier, adjuvant or vehicle.") will also indicate the allowability of the subject matter of the Examiner's Group III (as defined by claim 17 - "A therapeutic HCV vaccine composition comprising a therapeutically effective amount of a combination of at least two HCV single or specific oligomeric envelope E1 proteins or parts thereof wherein said at least two E1 proteins or parts thereof are derived from different HCV genotypes, subtypes or isolates; and at least one of a pharmaceutically acceptable carrier, adjuvant or vehicle. "). That is, the addition of at least one additional E1 protein or part thereof to the vaccine of claim 16, even if derived from a different HCV genotype, subtype or isolate, as recited in claim 17, will not require an additional search of the art since patentability may be based on the allowability of the at least one HCV E1 protein or a part thereof of claim 16.

Moreover, just as restriction between the Examiner's Groups I and II may have limited the applicants opportunity to amend the claims during prosecution as, for example, the subject matter of claim 16 is an embodiment of claim 15, requirement of restriction between the subject matter of the Examiner's Groups I and II, and the Examiner's Group III may also limit the applicants opportunity to amend the claims during prosecution as, for example, the subject matter of claim 17 is an embodiment of the subject matter of claims 15 (i.e., Group I) and claim 16 (i.e., Group II). The Examiner is urged to appreciate that claim 16 provides a vaccine composition which comprises at least one HCV envelope E1 protein or a part thereof.

Further, the Examiner has rejected claims 15 and 16, among other claims, as allegedly being obvious in view of claims 16 and 21 of the Assignee's prior U.S. Patent No. 6,635,257. See, page 9 of the Office Action dated January 15, 2004. The Examiner is urged to appreciate that claim 16 of the cited patent provides a composition comprising an oligomeric particle of claim 1, 7, 9, 10 or 11 of the cited patent and at least one of an excipient, diluent, carrier or adjuvant. Claim 11 of the cited patent, from which claim 16 of the cited patent depends, provides an oligomeric particle consisting essentially of HCV envelope proteins and having a diameter of 1 to 100 nanometer, wherein said envelope proteins, or parts thereof, are a mixture consisting of HCV envelope proteins from one strain or genotype of HCV and at least one other strain or genotype of HCV. Accordingly, to the extent the Examiner believes the present claims 15 and 16, which define the subject matter of the present Examiner's Groups I and II, are obvious in view of claim 16 of the cited patent, the subject mater of a composition containing a combination of envelope proteins from at least two strains or genotypes of HCV, as recited in claims 11 and 16 of the cited patent and claim 17 of the present application (i.e., Group III of the present application), does not define an independent and distinct invention and the subject matter of the Examiner's Group III should be examined with the subject matter of the Examiner's Groups I and II. The Examiner's restriction requirement is submitted, with due respect, to be inconsistent with the Examiner's double patenting rejection as well as the Patent Office's prior examination of the assignee's prior U.S. Patent No. 6,635,257.

Examination of all the subject matter of the Examiner's Groups I-III in a new non-final Office Action is requested.

Finally, the Examiner's withdrawal of claims 41 and 42 from consideration as being included in the subject matter of the Examiner's Group III is not understood as these claims depend from claims 23 and 24, respectively, which the Examiner has included in the subject matter of the Examiner's Group II, and substantively examined. Claims 41 and 42 further specify that the mammal recited in claims 23 and 24. respectively, is a human. Claims 41 and 42 are submitted to be improperly included in the subject matter of the Examiner's Group III. Examination of claims 41 and 42 with the subject matter of the Examiner's Groups I and II is requested.

A Rule 181 Petition is filed herewith for consideration by the Commissioner in the event the Examiner again refuses to consider all of the subject matter of the Examiner's Groups I-III together and/or examine the subject matter of claims 41 and 42 with the subject matter of the Examiner's Groups I and II.

Consideration of the attached Rule 181 Petition and a Decision on the same prior to issuance of a further Action from the Examiner is requested as issuance of a further Action prior to a Decision on the attached will likely prejudice the applicants in continuing prosecution, likely with the issuance of a final rejection which will close prosecution prior to receiving the benefit of the Commissioner's Decision which may change the subject matter which is to be examined. In such circumstances, the applicants are put in the position of either responding to a final rejection where the issue of the subject matter to be examined is still pending before the Commissioner or await the Commissioner's Decision prior to responding to the likely final rejection. In either case, the applicants will likely be required to at least pay for extension fees while awaiting the Commissioner's Decision. A Decision on the attached Petition is requested

prior to the issuance of a further substantive Action from the Examiner in the event the Examiner continues in refusing to examine the subject matter of the Examiner's Groups I-III in a single application.

Rejoinder of the process claims at an appropriate time is requested.

The Examiner's "requirement" stated in ¶4. of the Office Action dated January 15, 2004, to amend claim 15 "with a defined structure of the product that is comprised in the claimed composition" is noted. The Examiner is respectfully requested however to provide a specific rejection or objection of claim 15 based on some statutory provision or Rule as the basis for such a requirement, in which case the applicants will consider the appropriateness of such an amendment.

Reconsideration and withdrawal of the objection to the specification noted in ¶10 of the Office Action dated January 15, 2004, is requested in view of the following.

The specification has been further amended in response to the Examiner's comment in ¶12 of the Office Action dated January 15, 2004, to consolidate the recitation of the cross-reference to the earlier-filed priority applications filed November 29, 2001, and to include the issued patent number of the parent application. No new matter has been added.

The Examiner is urged to appreciate that the recited "E1s" has been described throughout the current specification, was known in the art prior as of the applicants' earliest claimed priority application and is moreover cited at least once in each of the priority documents and provisional applications. Specifically, the Examiner is requested to see, for example, Table 1, on page 29 of U.S. Patent application publication No. 2003/0118603 (publication of the current application) which describes "E1s" on at least

6 occasions; Example 15, ¶[0524] of U.S. Patent application publication No. 2003/0118603 states "The HCV E1s protein (amino acids 192-326)", and Examples 12 and 13 of U.S. Patent application publication No. 2003/0118603 which describe in paragraphs [0508] and [0515], respectively, "...with E1 (aa 192-326)" and further refer to Table 2 of WO 99/67285. The heading of Table 2 of WO 99/67285 (copy enclosed herewith and listed separately on the attached PTO 1449 Form) is "The E1s vaccine sequence aligned with...". Moreover, Example 18 of U.S. Patent application publication No. 2003/0118603 describes, in paragraph [0542], overlapping 20-mer peptides "covering the entire sequence of E1s".

For completeness, the applicants note that the term "E1s" is described in WO 99/67285 (which was filed as PCT/EP99/04342, priority of which is claimed in the present application), and more specifically on page 3, line 11 and in Example 1. These explanations were also present in the two EP priority applications EP 98 870 142.1 (page 3, line 7 and Example 1) and EP 99 870 033.0 (page 3, line 9 and Example 1)

The Table below further indicates, for example, in the applicants view, the description of the term "E1s" in the different documents:

	US 6,150,134	EP 98 870 142.1	EP 99 870 033.0	PCT/EP99/04342
Table 1	√			
Example 12		√ (as Example 4)	√ (as Example 4)	√ (as Example 4)
Example 13		√ (as Example 5)	√ (as Example 5)	√ (as Example 5)
Example 18				

	US 60/304,194	US 60/260,669	US 60/315,768
Table 1	√	√	√
Example 12		√	√
Example 13		√	√
Example 18			√

The term E1s is described throughout the present application, the claimed priority applications and was well known in the art.

Moreover, support for the presently claimed invention may be found throughout the present and priority applications. Specifically, support in EP 98 870 142.1, may be found, for example, at page 3, lines 4-13 and Examples 4-6 as well as Table 3; support in EP 99 870 033.0 may be found, for example, at page 3, lines 6-15 and Examples 4-6, as well as Table 3; support in PCT/EP99/04342 may be found, for example, at page 3, lines 7-17 and Examples 4-6, as well as Table 3; support in US application Serial No. 60/304,194 may be found, for example, in Example 11 and the claims; support in US application Serial No. 60/260,669 may be found, for example, in Examples 11-16 and the claims; and support in US application Serial No. 60/315,768 may be found, for example, in the Examples 11-18 and the claims. The pending claims are supported by the priority documents and the Examiner is requested to specifically accord benefit of the priority filing dates.

The Section 112, second paragraph, rejection of claims 15, 16, 18, 20-26, 36-39 and 40 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

Claim 15 is submitted to be definite. The applicants respectfully submit that they have described a <u>therapeutic</u> HCV vaccine compositions and that one of ordinary skill will appreciate the metes and bounds of the claimed composition. The applicants submit that the art has failed to demonstrate the therapeutic efficacy of any HCV vaccine and that the applicants demonstration of the same should afford broad protection.

The objected-to recitation of "part thereof" is also submitted to be sufficiently clear for one of ordinary skill in the art, especially in view of the present disclosure. One of ordinary skill in the art will appreciate that the definition of HCV envelope protein includes the "part thereof" as being at least one epitope of either the E1 or the E2 region, in the present case the E1 region. The recitation "part thereof" therefore is submitted to be sufficiently clear.

As for the Examiner's objection to the term "derived", the applicants also submit that the same is sufficiently clear to one of ordinary skill in the art. Specifically, one of ordinary skill in the art will appreciate that the objected-to term of, for example, claims 38 and 39 is the same as the meaning of "derived" in claims 23 and 24 which were not rejected on this basis. Moreover, the Examiner is requested to see, for example, the second sentence of paragraph [0178], "Cocktails..." of the published application, paragraph [0412] of the published application, in Example 2.3, the first sentence of paragraph [0464] of the published application, as well as to the first sentence of paragraph [0508] of the published application, in Example 12.

The claims are submitted to be definite and withdrawal of the Section 112, second paragraph rejection, is requested.

The Section 112, first paragraph "enablement", rejection of claims 15 and 16 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

Initially, the applicants note that the invention of claims 15 and 16 provide a therapeutic vaccine. Claim 16 specifically requires the presence of an envelope E1 protein or a part thereof.

Moreover, the Examiner has indicated in the obviousness-type double patenting rejection referred to above, that claims 15 and 16, as well as other claims, would have been obvious in view of a previously issued claims to compositions of oligomeric particles consisting essentially of HCV envelope proteins. To the extent the Examiner's remarks may be contrary to the Patent Office's prior position of patentability of the applicants claims in the parent U.S. Patent No. 6,635,257, signature by the Group Director is believed to be required. At a minimum, the Examiner's Section 112, first paragraph "enablement", rejection of claims 15 and 16 is believed to be contrary to the obviousness-type double patenting rejection of claims 15 and 16 over claims 16 and 21 of the previously granted patent.

Similarly, the Section 112, first paragraph "enablement", rejection of claims 15 and 16 is believed to be contrary to any one of the following:

the Section 102 rejection of claims 15 and 16 over WO96/04385A2, which the Examiner describes on page 11 of the Office Action of January 15, 2004 as disclosing a

> "composition comprising purified recombinant HCV oligomeric recombinant envelope protein selected from the group consisting of E1 and/or E2 or E1/E2 expressed by mammalian cell or yeast, wherein both E1 and E2 glycosylation sites can be mutated to increase the immunogenicity (See pages 58-62). The composition further comprises a pharmaceutically acceptable adjuvant used as a medicament or vaccine for immunizing human against HCV infection (see claims 11, 36, 37, 38 and 39). Therefore, claimed invention is anticipated by the reference.";

the Section 102 rejection of claims 15 and 16 over Choo (PNAS 1994, vol 91, pp 1294-1298) which the Examiner describes on page 11 of the Office Action of January 15, 2004 as disclosing

> "administration of a composition comprising a recombinant HCV envelope glycoprotein E1 and an adjuvant into Chimpanzee animals [to induce] ... a humoral immune response and get a partial protection conferred by the HCV-1 vaccine against the heterologous clinical isolate of HCV infection (See pages 1295-1296).";

the Section 102 rejection of claims 15 and 16 over Houghton et al (Prospects for prophylactic and therapeutic hepatitis C virus vaccines. Princess Takamatsa Symp. 1995, vol 25, pp 237-243) which the Examiner describes on page 11 of the Office Action of January 15, 2004 as disclosing

> "that administration of a composition comprising a recombinant HCV envelope glycoprotein E1 expressed by Hela cells into Chimpanzee animals induces a humoral immune response and get a partial protection conferred by the HCV-1 vaccine against the heterologous clinical isolated HCV infection (See pages 239-240).";

the Section 102 rejection of claims 15 and 16 over Houghton et al (Proceedings of IX Triennial International Symposium on Viral Hepatitis and Liver Disease, Rizettp Purcell, Gerin, Verme, eds., Edizioni Minerva Medica, Italy, 1997, pp. 656-657) which the Examiner describes on page 11 of the Office Action of January 15, 2004 as disclosing

> "that administration of a subunit of HCV vaccine comprising a recombinant HCV envelope glycoprotein E1/E2 expressed by Hela cells into Chimpanzee animals. Four out of six immunized chimpanzees get a complete protection and two out of six chimpanzees produce a less severe acute hepatitis (See pages 657 [sic])."; and/or

the Section 102 rejection of claims 15 and 16 over Weiner (U.S. Patent No. 5,670,152) which the Examiner describes on page 12 of the Office Action of January 15, 2004 as disclosing

> "an immunogenic composition comprising purified HCV envelope polypeptide derived from distinct HCV isolates including HCV group I and HCV group III (See claims 1-9), wherein the composition is disclosed for using [sic] as a vaccine as well as therapeutic composition for treating HCV infection (See lines 6-19 on col. 28)."

The Examiner is requested to either withdraw the Section 102 rejections of claims 15 and 16 or withdraw the Section 112, first paragraph "enablement", rejection of claims 15 and 16.

Specifically, the applicants submit that if the art does, in fact, place the presently claimed invention in the art, as the Examiner asserts in the Section 102 rejections of claims 15 and 16, then one of ordinary skill is presumably also taught how to make and use the claimed compositions and methods and the Section 112, first paragraph, rejection should be withdrawn. Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research, 68 USPQ2d 1373, 1375 (CA FC 2003) ("To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). *See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make

the anticipating subject matter."). Alternatively, one of ordinary skill is not taught by the art how to make and use the claimed invention, in which case the Section 102 rejection should be withdrawn, and the question remains as to whether the specification teaches how to make and use the claimed invention (i.e., does the specification provide enabling support when taken with what is known in the art).

Reconsideration and withdrawal of the Section 102 rejections and the Section 112, first paragraph "enablement", rejection of claims 15 and 16 are requested.

Consideration of the following is also requested in specific response to the Examiner's comments on pages 7-9 of the Office Action dated January 15, 2004.

State of the Art.

The Examiner's apparent requirement for regulatory approval (i.e., "approved as a HCV vaccine") as a prerequisite of demonstrating enablement is not a standard required by the courts for establishing that a specification provides enabling support. As noted above, if the Examiner believes the cited art anticipates the invention of claims 15 and 16 then one of ordinary skill in the art was able to make and use the claimed invention from the teachings of that same art. One of ordinary skill in the art is able to make and use the presently claimed invention without undue experimentation.

The Examiner relies on Liang et al. (Ann Intern Med (2000)132:296-305) to allegedly support the Examiner's position that development of HCV vaccines "is extremely unpredictable." See, the list of five enumerated "problems" recited by the Examiner on page 7 of the Office Action dated January 15, 2004. Again, contrary to the Examiner's reliance on the cited art to allege the art anticipated the invention of claims 15 and 16, the Examiner asserts that Liang, which was published after the allegedly

anticipatory art, indicates that one of ordinary skill in the art could not make and use the invention of claims 15 and 16.

The applicants submit, with due respect, that the state of the art is more developed than the Liang et al. and Ghany et al. (Hepatology 2003, vol. 38, pp. 1289-1296) references relied upon by the Examiner. The following is submitted as a more complete reflection of the state of the art, the number of working examples and amount of guidance.

The T-cell stimulation properties of HCV envelope proteins and fragments thereof is well-known in the art, both for E1 and E2.

The Examiner is requested to see in this regard International Patent Publication No WO 95/12677 which discloses the T-cell stimulating properties of synthetic E1-, E2-, NS3- and Core peptides of HCV. The Examiner is further requested to see also U.S. Patent No. 6,613,333. From Tables 4-6 in this patent/patent application one of ordinary skill in the art will appreciate that E1 and/or E2 peptides of a single HCV isolate of type 1a or 1b are in most cases able to elicit stimulation of T-cells isolated from patients infected with other (by definition variant) HCV isolates of type 1a or 1b and even of T-cells isolated from patients infected with HCV isolates of other genotypes (3a, 4a or 5a). That is, the applicants submit that one of ordinary skill in the art will appreciate that despite the sequence variation between HCV isolates, -subtypes and -types, cross-reactivity at the T-cell level has been proven.

Botarelli et al. 1993 (Gastroenterology 104, 580-587; copy attached and listed on the attached PTO 1449 Form) analyzed the T-cell response of Core, E1, E2, NS3-4, NS4 and NS5 produced as SOD fusion proteins in Saccharomyces.

International Patent Publication No WO 99/67285 (from which priority is claimed), and more specifically Examples 4 and 5 therein (i.e., Examples 12 and 13 of the current invention), illustrates that both homologous and heterologous T-cell responses can be elicited in HCV-infected chimpanzees.

International Patent Publication No WO 03/051912, and more specifically Example 19 therein, illustrates that immunization of chronically HCV-infected humans with the HCV envelope protein-based vaccine leads to induction of a cellular (T-cell) response as well as of a humoral (antibodies) response.

WO 95/12677 illustrates and contradicts the statement of the Examiner made at the end of ¶25 of the Office Action dated January 15, 2004 that T-cell epitopes should be targeted in the conserved Core, NS3, and NS4 regions.

WO 99/67285 and WO 03/051912 clearly illustrate that HCV envelope proteins do not inhibit the induction of a cellular immune response, in contradiction to the last sentence of ¶ 27 of the Office Action dated January 15, 2004.

Vaccine activity

International Patent Publication No WO 99/67285 (from which priority is claimed), and more specifically Examples 4 and 5 therein (i.e., Examples 12 and 13 of the current application). These Examples illustrate that HCV envelope proteins were used successfully to treat both homologous and heterologous HCV infection in the accepted chimpanzee model (therapeutic vaccine). More specifically, the observed beneficial effects of the HCV vaccine included induction of a higher and longer lasting anti-envelope antibody response (relative to the response normally observed in chronic HCV

carriers), decrease of liver enzyme (e.g., ALT) activity in the serum, the decrease of HCV antigen staining in liver tissue and decrease of liver inflammation.

The therapeutic effects of the HCV envelope protein-based vaccine observed in chimpanzees were confirmed in and extended to chronically HCV-infected humans as outlined in Examples 19-21 of International Patent Publication No WO 03/051912. The confirmation included the immunological response (not only antibody response but also T-cell stimulation), the serum liver enzyme response, the decreased HCV antigen staining in liver tissue. The therapeutic effects of the HCV vaccine were furthermore extended to the halting and even the reversion of liver fibrosis. The latter beneficial effect can moreover not be followed up in chimpanzees as chimpanzees only develop very limited liver fibrosis during HCV infection. These data have also been published by Leroux-Roels et al. 2001 (Hepatology 34, 449A), Nevens et al. 2003 (Hepatology 38, 1289-1296), and Pawlotsky and McHutchison 2003 (Hepatology 39, 554-567, more specifically pages 563-564). Copies of all these references are enclosed and listed on the attached PTO 1449 Form.

In specific response to the Examiner's comments from Liang, and the alleged unpredictability of the making and using the claimed invention, the applicants offer the following:

a) "...the virus exists as a quasi-species because of a high rate of mutation in the hypervariable region of the envelope proteins." See, page 7 of the Office Action dated January 15, 2004.

With all due respect, the applicants submit that the Examiner appears to be confusing two distinct concepts of HCV virology.

The quasi-species concept applies to HCV but is certainly not restricted to the occurrence of mutations only in the hypervariable region (HVR) of the envelope proteins. The whole HCV genome is prone to mutations due to a lack of proofreading activity of the viral replicase. This is even occurring within a single host, i.e., HCV exists as a quasi-species within a single host. Note that even an HCV inoculum used for challenge infection in fact contains an HCV quasispecies. Nevertheless successful immune responses can be generated and protect a challenged vaccinee from developing chronic HCV disease, as discussed above.

The hypervariable region concept is for HCV mainly, if not only, applicable to the E2 envelope protein and refers to a large degree of sequence variation in the E2 HVRs between different HCV subtypes or –genotypes.

Notwithstanding the "unpredictability" argument of the Examiner due to the variation between HCV sequences, the data described above illustrate the existence of cross-reactivity in terms of antibody response, T-cell response and vaccine efficacy. The degree of unpredictability thus is submitted to be not as "extreme" as the Examiner is suggesting.

b) "...the hypervariable region of envelope proteins contains a principal neutralization epitope responsible for inducing the neutralizing antibody." Id.

As the Examiner correctly indicated, HVRI of E2 is a major site of anti-E2 antibody response and contains a principal neutralization epitope. This is actually an argument in favor of, not against, the use of HCV envelope proteins in a vaccine setting.

Both listed characteristics are highly desirable for a subunit HCV vaccine. The possibility of raising neutralizing antibodies against HCV moreover opens the route to complete neutralization of HCV virions. The advantage of raising anti-envelope antibodies is explained in more detail in the following.

c) "...the neutralizing antibody of HCV E1 or E2 develop slowly and achieve only modest titers..." Id.

The slow development and low levels of antibodies may be true during the natural course of HCV infection. Active immunization with the applicant's HCV envelope protein-based vaccine is, however, overcoming this problem. From the data described above in above, one of ordinary skill in the art will appreciate that sufficient levels of anti-envelope antibodies can be raised with an HCV envelope protein-based vaccine. These antibody levels are higher and longer lasting anti-envelope antibody response (relative to the response normally observed in chronic HCV carriers; see Examples 4 and 5 in WO 99/67285 from which priority is claimed, i.e., Examples 12 and 13 in the current application). The antibody levels are in addition sufficiently high to stop or reverse adverse symptoms related to HCV infection, in particular liver fibrosis caused by HCV infection. Moreover, the degree with which liver disease is halted or reverted correlates with the level of anti-envelope antibodies raised in a patient (see Examples 19-21 in WO03/051912).

The conclusions of the Examiner and reliance on Liang et al are therefore submitted to be incorrect and misplaced.

d) "...immunologic responses that correlate with the HCV protection and disease progression have not been clearly defined." Id.

The applicants have responded to this argument above. The applicants believe that an immunologic correlate has been defined. It was moreover only possible to establish this correlate in humans, as opposed to the chimpanzee model-animal.

The argument relating to an alleged further complication of finding a correlate due to the inexistence of suitable in vitro systems does not appear to be relevant as the Examiner admits that in the Examiner's opinion the chimpanzee is the only accepted model system. As to the alleged lack of protective immunity in chimpanzees after natural infection and natural/spontaneous clearance of infection the following counterarguments are given:

As indicated by the Examiner, the increase in antibody response to HCV envelope proteins is slow, albeit during natural infection. The applicants have, however, shown that active immunization is overcoming this problem, as noted above.

Many studies indicate that chimpanzees naturally/spontaneously recovering from a primary HCV infection clear a secondary HCV infection again and very often clear this secondary HCV infection more rapidly than the primary HCV infection (Major et al. 2002, J Virol 76, 6586-6595; Basset et al. 2001, Hepatology 33, 1479-1487; Weiner et al. 2001, J Virol 75, 7142-7148; copies of references attached and listed on the attached PTO 1449 Form). Similarly and moreover, protection to persistent HCV infection has been documented in humans who previously spontaneously resolved HCV infection (Mehta et al. 2002, Lancet 359, 1478-1483; copy attached and listed on the attached PTO 1449 Form).

The Examiner's argument relating to the absence of protective immunity after immunization seems to be contradicted by the Examiner in ¶¶ 41-48 of the Office Action

dated January 15, 2004. In addition, the presently claimed invention relate to a **therapeutic** HCV vaccine and not to a prophylactic HCV vaccine. Hence, this argument is not believed to be relevant.

With regards to the cited Ghany et al. (2003) reference, the applicants note that Ghany et al is merely an editorial comment on a clinical development. The "recommendation" by Ghany et al. concerning not using the HCV envelope protein-based vaccine of the current invention is not unexpected and, more importantly, as note above, the recommendations of a clinician or scientist to adopt a therapy, such as would be the result of regulatory approval, is not the standard for enablement required by the Patent Law.

In fact, the applicants believe that such editorial comments usually accompany promising results of investigational therapies to caution clinicians that the reported results are not yet approved or recommended as a standard treatment or therapy. That the applicants current developments have attracted a great amount of interest can be seen from, e.g., the fact that a summary of the Nevens et al. (2003) publication (to which the Ghany et al. (2003) editorial is directed) has appeared for several months at the Gastroenterology homepage of Medscape, one of the most visited and most subscribed medical websites worldwide. It should be clear, however, a patent prosecution procedure which must be based on unbiased and fair interpretation of the contents of a patent application and that a patent prosecution procedure is separate and distinct, with different standards, from any FDA guidelines and practices or regulatory approval.

Moreover, the applicants believe that enablement does not require production of an ideal HCV vaccine to teach one of ordinary skill in the art to make and use the claimed invention. Rather, the first goal to be achieved in the HCV vaccine field is the establishment of a first working and effective HCV vaccine. Clearly, such a first HCV vaccine may not be the ideal HCV vaccine the Examiner has in mind and may of course be the subject of further improvement. The applicants have achieved at least this first important milestone as is apparent from the current and earlier filed, co-pending patent applications.

In fact, the U.S. patent Examiner in the applicants' Assignees' copending application Serial No. 10/128,578 (which published as U.S. patent application publication No. 2003/0211597A1 - a copy of the publication and electronic file of the copending application are believed to be available to the Examiner such that copies of the same are not being provided herewith however the Examiner is requested to advise the undersigned if a copy of the same should be submitted) has acknowledged that the specification of the co-pending application teaches a therapeutic HCV vaccine. Specifically, the Examiner of the co-pending application as stated as follows:

> "The term "vaccine" generally is used to mean a composition which induces an immune response protective against disease. The specification provides evidence that a sulfonated E1 particle (reversibly modified) is able to induce antibodies. The specification also asserts that an alkylated E1 protein produced by expression from vaccinia virus in mammalian cells vaccinia-expressed was protective in a prophylactic vaccine study and a therapeutic vaccination study, and provides evidence that sera from those animals was able to cross-reactive with alkylated yeast-produced EI (irreversibly modified)." See, Office Action dated June 22, 2004.

The present Examiner is requested to appreciate that regulatory approval is not required to demonstrate that a disclosure teaches one of ordinary skill in the art how to make and use a therapeutic vaccine.

With regard to the comments of ¶27 of the Office Action dated January 15, 2004, the applicants again respectfully note that the presently claimed invention relates to a **therapeutic** HCV vaccine, and not to a prophylactic HCV vaccine. Moreover, as discussed above, at least Examples 12 and 13 of the current application illustrate therapeutic vaccine activity of, and the elicitation of T-cell responses by, the HCV envelope protein-based therapeutic vaccine of the current invention.

Successful initial trials -both therapeutic and prophylactic- were performed with the HCV envelope protein-based vaccine on the accepted chimpanzee animal model. The therapeutic outcome of the chimpanzee-trial was, and is, being confirmed and extended in ever larger clinical trials on human patients. The applicants believe that it should be clear to the present Examiner that HCV challenge infections in humans will not be accepted by any Regulatory Body or Ethic Committee.

Based on the totality of the above remarks, the applicants submit that the claims are supported by an enabling disclosure. The applicants have demonstrated a significant milestone in the HCV vaccine field.

Despite the high level of skill in the field and the complexity of the field, the applicants submit that they have succeeded where others have previously failed.

Withdrawal of the Section 112, first paragraph "enablement", rejection of claims 15 and 16 is requested.

The Examiner is requested to hold the obviousness-type double patenting rejection of claims 15, 16, 18, 21-26 and 36-39 over claims 16 and 21 of U.S. Patent No. 6,635,257, and the provisional obviousness-type double patenting rejection of claims 15, 16, 18, 21-26, 36-39 and 40 over claims 1, 2, 3, 5, 7, 9, 10, 11, 12, 13 and 14 of application Serial No. 09/995,791, in abeyance until such time as allowable subject matter is identified, at which time the applicants will consider whether filing a Terminal Disclaimer is appropriate.

The Section 102 rejection of claims 15, 16, 18, 21-26, 36-39 and 40 over WO96/04385A2, is traversed. Withdrawal of the rejection is requested in view of the Examiner's comments relating to the requirements for enablement. Liang et al., according to the Examiner, demonstrates that the cited reference fails to teach one of ordinary skill in the art to make and/or use the claimed invention. For completeness, the applicants attach a copy of the pending claims of the co-pending application Serial No. 08/928,757. Acknowledgement of the consideration of the attached claims in the Examiner's next Communication is requested along with withdrawal of the Section 102 rejection.

The Section 102 rejection of claims 15, 16, 18 and 36 over Choo (PNAS 1994, vol 91, pp 1294-1298) is traversed. Withdrawal of the rejection is requested in view of the Examiner's comments relating to the requirements for enablement. Liang et al., according to the Examiner, demonstrates that the cited reference fails to teach one of ordinary skill in the art to make and/or use the claimed invention.

The Section 102 rejection of claims 15, 16, 18 and 36 over Houghton et al (Prospects for prophylactic and therapeutic hepatitis C virus vaccines. Princess

Takamatsa Symp. 1995, vol 25, pp 237-243) is traversed. Withdrawal of the rejection is requested in view of the Examiner's comments relating to the requirements for enablement. Liang et al., according to the Examiner, demonstrates that the cited reference fails to teach one of ordinary skill in the art to make and/or use the claimed invention. Moreover, the cited Houghton et al (1995) reference relates, at best, to a prophylactic vaccine effect of a purified envelope complex. See, page 238 of the reference ("The purified envelope complex was then combined with an oil/water microemulsion adjuvant along with the immunostimulator muramyl tripeptide and used to immunize 7 uninfected chimpanzees by repeated intramuscular injection (Choo et al. 1994 [PNAS **91** 1294-1298 February 1994 - of record]). Two to three weeks following the final immunization, the animals were challenged i.v. with 10 chimpanzee infectious doses (CID_{50}) of homologous HCV-1..." (emphasis added)). The Houghton et al. (1995) reference fails to teach a therapeutic HCV vaccine composition or method of the presently claimed invention.

The cited Houghton et al (1995) reference further admits that "no vaccine efficacy has been observed" in a separate study of "immunization of chimpanzees persistently infected with strain HCV-H with the HCV-1 E1/E2 vaccine." See, page 241, first two sentences, of the Houghton et al. (1995) reference.

Withdrawal of the Section 102 rejection of claims 15, 16, 18 and 36 over Houghton et al (Prospects for prophylactic and therapeutic hepatitis C virus vaccines. Princess Takamatsa Symp. 1995, vol 25, pp 237-243) is requested.

The Section 102 rejection of claims 15, 16, 18 and 36 over Houghton et al (Proceedings of IX Triennial International Symposium on Viral Hepatitis and Liver

Disease, Rizettp Purcell, Gerin, Verme, eds., Edizioni Minerva Medica, Italy, 1997, pp. 656-657) is traversed. Withdrawal of the rejection is requested in view of the Examiner's comments relating to the requirements for enablement. Liang et al., according to the Examiner, demonstrates that the cited reference fails to teach one of ordinary skill in the art to make and/or use the claimed invention.

The cited Houghton et al. (1997) reference is a further report of the studies reported in the Houghton et al. (1995) reference discussed above. Both the cited Houghton et al. (1995) and (1997) references describe, essentially, the study reported in Choo et al. (1994) of record. The present Examiner has found the presently claimed invention patentable over Choo et al. (1994). The present claims are patentable over the Houghton et al. (1997) reference for reasons described above with regard to the Houghton et al. (1995) reference. Moreover, Houghton et al. (1997) concludes on page 658, in describing "**The future**" that one of the "Several key issues [which] remain to be established" is "the potential efficacy of the subunit vaccine in the therapeutic mode [which] deserves attention." Emphasis added. Houghton et al. (1997) fails to teach a therapeutic vaccine composition or method of the present claims.

Withdrawal of the Section 102 rejection of claims 15, 16, 18 and 36 over Houghton et al (Proceedings of IX Triennial International Symposium on Viral Hepatitis and Liver Disease, Rizettp Purcell, Gerin, Verme, eds., Edizioni Minerva Medica, Italy, 1997, pp. 656-657) is requested.

The Section 102 rejection of claims 15, 16, 18, 36 and 40 over Weiner (U.S. Patent No. 5,670,152) is traversed. Withdrawal of the rejection is requested in view of the Examiner's comments relating to the requirements for enablement. Liang et al.,

according to the Examiner, demonstrates that the cited reference fails to teach one of ordinary skill in the art to make and/or use the claimed invention. Moreover, Weiner's co-inventor is Michael Houghton, who is believed to be the same Houghton of the above-discussed references which were published in 1995 and 1997. Weiner et al describes work filed September 1991. Houghton's comments of the 1995 and 1997 references are submitted to be evidence that Weiner et al fails to describe a therapeutic vaccine composition in 1991. The claims are submitted to be patentable over Weiner et al.

Withdrawal of the Section 102 rejection of claims 15, 16, 18, 36 and 40 over Weiner (U.S. Patent No. 5,670,152) is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100